High Rate of Advanced Adenoma Detection in 4 Rounds of Colorectal Cancer Screening With the Fecal Immunochemical Test

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BACKGROUND & AIMS: Few data have been published on the performance of colorectal cancer (CRC) screens that use multiple rounds of the fecal immunochemical test (FIT). We evaluated outcomes of 4 screening rounds in over 7 years in an Italian population-based program. **METHODS:** We conducted a prospective cohort study of 2959 average-risk subjects, aged 50–74 years, who were invited for the first screening round in 2001. We assessed the participation rate, the yield of advanced adenomas and CRC detected in the screening examinations, and we collected information about interval CRCs, with a follow-up period of 8.5 years. **RESULTS:** Participation in each round varied from 56% to 63%; 48.1% of eligible subjects attended all 4 invitations. The positive predictive value of the FIT for advanced neoplasia (CRC or advanced adenoma) was 40% at the first round, and approximately 33% in the subsequent rounds. This decrease was attributable mainly to a decrease in the detection of CRC, although a high rate of advanced adenomas (range, 0.8%–1.7%) was observed over all rounds. To find one advanced neoplasia in the study period the number of people that needed to be screened was 28, and the number of tests needed was 74. **CONCLUSIONS: About 60% of invited individuals participated in every single round of FIT screening for CRC, but less than 50% attended all 4 tests. A high detection rate of advanced adenomas in all rounds indicates that FIT screening could have a higher impact on incidence of CRC than the guaiac fecal occult blood test.**

Keywords: Colon Cancer; Early Detection; FOBT; Diagnostic.

The efficacy of screening strategies based on fecal occult blood testing (FOBT) in reducing colorectal cancer (CRC) mortality has been established in randomized controlled trials using the guaiac-fecal occult blood test (gFOBT).[1] A reduction of the CRC incidence, probably attributable to the removal of adenomatous polyps among people with gFOBT positive test undergoing colonoscopy, was reported in one study.[2] CRC screening is now running or being performed in 19 of 27 European countries.[3] Biennial gFOBT was introduced in some European countries,[3] whereas in Italy all programs adopted a biennial fecal immunochemical test (FIT).[4] Recent reports have shown that, compared with gFOBT, FIT screening is associated both with a higher acceptance and higher detection rate of CRC and advanced adenomas.[5–9] As a consequence of this evidence, FITs recently were recommended as the fecal test of choice for population-based programs.[3]

There is, however, limited experience regarding the results achievable with FIT screening over several rounds in terms of attendance, positivity rates, and yield of neoplasia.

The present study was undertaken to describe the outcomes of a CRC population screening program in a cohort of people who were offered 4 FIT invitations.

Methods

Study Population

We conducted a prospective cohort study among people enrolled in a population-based screening program for CRC, in the municipalities of Chatillon and St. Vincent, in the Aosta Valley Region in Italy. In these two municipalities, a pilot study was started in 2001 and repeated in 2003, aimed at evaluating the feasibility of a program using biennial FIT.[10] All subjects enrolled in the pilot study in 2001 and 2003 were invited again (if still eligible) in 2006 and 2008, in the context of the regional screening program offering all residents the same FIT test. This cohort of people, invited 4 times over 7 years, was included in the analysis.

Invitation

All residents in the study area, aged 50–74 years, identified through the Regional Health Service register, were targeted for recruitment in the screening pilot in 2001. Subjects older than age 74 at the beginning of each round were excluded from invitation. General practitioners (GPs) were involved in the organization of screening and were asked to exclude their patients with a personal history of polyps or CRC and inflammatory bowel disease. People reporting recent colorectal endoscopy (within the previous 5 years), or FOBT (within the previous 2 years), and patients with terminal illness or unable to provide their consent also were excluded. Eligible people were mailed a personal invitation letter, signed by their GP, accom-

Abbreviations used in this paper: AN, advanced neoplasia; AR, attendance rate; CI, confidence interval; CRC, colorectal cancer; DR, detection rate; FIT, fecal immunochemical test; FOBT, fecal occult blood test; gFOBT, guaiac-fecal occult blood test; GP, general practitioner; NNS, number needed to screen; PPV, positive predictive value; PR, positive rate; TC, total colonoscopy.

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panied by a leaflet providing information about CRC screening. The letters arranged for an appointment at a local municipal office where volunteers distributed the test kits, recording participants' demographic data on a delivery register. During this meeting participants were instructed orally on how to collect and to store refrigerated fecal samples and were requested to return the kits to the local pharmacy quickly after collection. In all screening rounds, a reminder was sent after 2 months to noncompliant participants with the first invitation and to subjects who collected but did not return their kits. Because of organizational problems, the starting date of the third round was delayed by 6 months (from November 2005 to April 2006).

Test Performance

After the findings of comparative studies conducted in Florence,[11,12] we adopted a quantitative FIT, based on latex agglutination (OC-Sensor; Eiken Chemical, Co, Tokyo, Japan), performed on a single sample, without dietary restrictions, with a positivity cut-off value set at 100 ng Hb/mL buffer. Returned samples were processed in a single central laboratory, using an automated procedure, following the manufacturer's instructions. The mean interval between collection and development of fecal samples was 3 days. Subjects with negative tests received a letter suggesting they repeat screening after 2 years and visit their GPs for any bowel complaint occurring during that period.

Management of Subjects With Positive Test Results

Subjects with positive FIT results were invited by telephone to undergo total colonoscopy (TC). We used routine sedation (meperidine 50 mg intravenously). Double-contrast barium enema (or computed tomography colonography starting in 2006) was undertaken when TC could not be completed to the cecum. The reach of the scope and the location of all lesions were recorded by the endoscopist on a standard form. If no neoplasia was found, the patient was invited to repeat FIT after 6 years. Individuals found to have CRC or adenoma were referred for endoscopic or surgical treatment and subsequently for endoscopic surveillance whenever appropriate. Almost all endoscopic and radiologic examinations, as well as surgical or endoscopic therapy, were performed in the same hospital. All removed polyps were judged by either 1 of the 2 pathologists from the Regional Hospital Pathology Department. Histologic classification of polyps and CRC was based on the World Health Organization criteria. Advanced adenomas were defined as those 10 mm or greater, or with high-grade dysplasia, or villous component greater than 20%. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosae. The term *advanced neoplasia* (AN) was used to define a CRC or advanced adenoma. Patients with in situ or intramucosal carcinoma were classified as having high-grade dysplasia. Each patient was classified based on the most advanced lesion.

Incidence Follow-up Evaluation

All subjects enrolled in October 2001 were actively followed up for an 8.5-year period until April 30, 2010. All CRCs diagnosed in the study cohort were identified through a record linkage of the study database with the regional hospital discharge records and with the archives of the Pathology Department of the Aosta Regional Hospital.

Analysis

For each screening round we calculated the attendance rate (AR), the positivity rate (PR), and the detection rate (DR) for CRC and adenoma. We also estimated, over the 4 rounds, the cumulative AR, measured as the proportion of subjects attending all invitations over those invited in all rounds. We calculated the PR and DR by the number of consecutive tests performed, the number of people needed to screen (NNS), and the number of tests performed to detect one AN. CRCs were classified, based on the subject's screening history, as screen detected, interval CRC, and CRC in subjects who never participated. Screen-detected CRCs are those diagnosed as a result of the investigations after a positive test. We calculated for all patients the interval since the last negative FIT. Interval cancers were defined as CRCs diagnosed within 2 years of a negative FIT.

We assessed the independent role of sex and age as predictors of regular attendance using a multivariate logistic regression model. Confidence intervals (CIs) for the proportions were calculated using the exact method; the chi square test was used to test the differences in AR and DR in the univariate analysis. All tests were 2-sided at $P < .05$ level for statistical significance.

Results

In October 2001, of 9800 inhabitants residing in the study area, 3145 people aged 50–74 years were identified through the Regional Health Service register. After excluding 186 subjects that GPs considered as being ineligible, 2959 people were invited to participate in the first screening round. As seen in Figure 1, 1862 people (62.9% of the initial cohort) were eligible to be invited in the fourth round in 2008. This reduction of the target population reflects mainly the progressive aging of the cohort. About 7% of people were excluded from invitation at the time of subsequent rounds because they were older than age 74, and an additional 5% were excluded because they could not be traced or had emigrated; FIT-positive subjects also were no longer invited.

Of 1862 people who received all 4 invitations, 1445 (77.6%) attended at least once, and 1177 (63.2%) and 902 (48.4%) had 2 and 3 consecutive tests, respectively. The proportion of regular attenders (subjects attending all the invitations) was 38.3% (713 of 1862). Even adding to this latter group those subjects with a positive FIT in previous rounds who were no longer eligible for invitation, the proportion of people who fully complied with the recommended screening protocol was 48.1% (95% CI, 45.8–50.4; 895 of 1862). The proportion of these regular attenders was the same for all age groups, although after adjusting for age the proportion was higher among women than among men (odds ratio, 1.35; 95% CI, 1.11–1.63). Moreover, in 4 rounds, 8.6% of the targeted subjects performed 2 nonconsecutive tests, whereas 10.5% participated just one time. The data concerning PR, compliance with TC referral, and neoplasia yield in each screening round are reported in Table 1. At each round the PR was about 4% and more than 90% of patients with a positive FIT accepted to undergo colonoscopy; the completion rate of the procedure ranged between 91% (in 2001) and 96% (in 2008).

Overall, of the cohort of 2959 people invited in 2001 (Table 2), 2161 (73.0%) performed at least 1 test, and 1520, 971, and 713 performed 2, 3, and 4 consecutive tests, respectively. The positive predictive value (PPV) for CRC and advanced adenomas

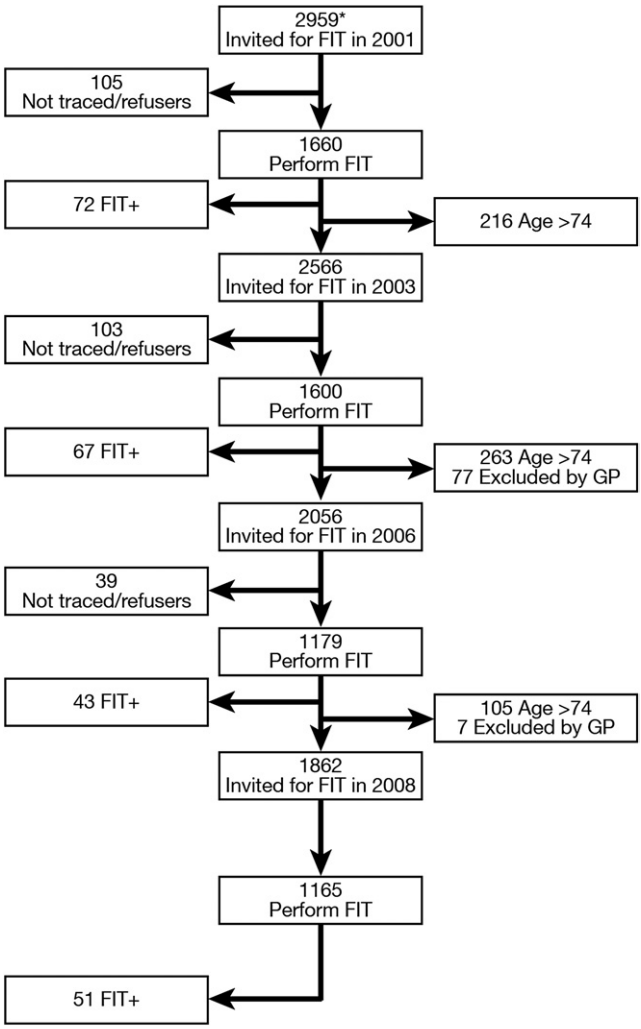

Figure 1. Four screening rounds flowchart.

remained stable after the prevalence screening. Taking into account individuals' screening history, the DR of CRC tended to decrease among people with several previous negative examinations, whereas such a trend was not observed for advanced adenomas: the proportion of FIT-positive subjects detected with an advanced adenoma was 34.5% at the first examination, and was still 33.3% after 3 negative tests.

Table 3 shows the cumulative number of tests and the cumulative DR of AN in people attending consecutive and nonconsecutive rounds. Of 2161 people attending at least once, the cumulative DR of AN was 3.5% (N = 76). In the prevalence round, 62 subjects had to be screened to detect one AN; this NNS, as well as the number of examinations to be performed for the same target, tended to increase with the number of previous negative examinations. Over 4 rounds, the NNS was 28 and the average number of tests was 74.

The median duration of the cohort follow-up evaluation was 103 months (range, 102–103 mo). Subjects invited in the fourth round had a median follow-up period of 23.6 months after their last invitation (range, 18–26 mo). Over the 8.5-year follow-up period, 32 CRCs were diagnosed among the 2959 people included in the study (Table 4). The cumulative CRC incidence was higher among those who never attended screening, with 14 cases occurring among 798 subjects (1.75%; 95% CI, 1.00–3.00), than among those attending at least one invitation, with 18 cases among 2161 people (0.83%; 95% CI, 0.51–1.34). Eight of these latter 18 cases were detected at screening (5 at the prevalence round and 3 at subsequent examinations) and 10 were detected among people who had performed at least one test. Five of these 10 cases could be classified as interval CRCs (3 after a negative FIT at the prevalent round and 2 at subsequent negative examinations); 3 of the remaining CRCs were detected at 16, 46, and 72 months after a negative TC prompted by a positive FIT, whereas the 2 remaining patients were diagnosed with a CRC 28 and 50 months after the last negative FIT. The CRCs diagnosed among people who never attended screening showed an unfavorable stage distribution as compared with those detected among people who participated at least once (71.4% vs 33.3% stage IV CRCs).

Discussion

The information concerning the performance of FIT screening over several rounds still is limited. We actively studied an average-risk population cohort, invited in 4 screening rounds, using an automated quantitative FIT. We observed a high response rate at each invitation, ranging between 56% and 63%, but the proportion of subjects who complied with all the recommended testing protocol was less than 50%. Fewer cases

Table 1. Positivity Rate and Detection Rate for Advanced Neoplasia by Screening Rounds in the Same Study Cohort

Screening round	2001	2003	2006	2008
Subjects examined, n	1660	1600	1179	1165
%	56.1	62.4	57.3	62.6
95% CI	54.3–57.9	60.4–64.2	55.2–59.5	60.3–64.8
Positivity, n	72	67	43	51
%	4.3	4.2	3.7	4.4
95% CI	3.4–5.4	3.3–5.3	2.7–4.9	3.3–5.8
Colonoscopy performed, n	67	60	39	48
%	93.1	89.6	90.7	94.1
DR advanced neoplasia, n[a]	25	21	15	15
%	1.51	1.31	1.27	1.29
95% CI	1.00–2.25	0.84–2.04	0.74–2.14	0.75–2.17

[a]Advanced adenoma and CRC.

Table 2. Positivity Rate, Detection Rate, and Positive Predictive Value of Advanced Adenoma and CRC by Number of Consecutive Tests Performed

Number of consecutive tests	1	2	3	4
People examined, n[a]	2161	1520	971	713
Positivity, n	92	62	33	36
%	4.3	4.1	3.4	5.1
95% CI	3.5–5.2	3.2–5.2	2.4–4.8	3.6–7.0
Colonoscopy performed, n	87	54	29	36
%	93.1	89.6	90.7	100
Advanced adenomas, n	30	17	8	12
Advanced adenomas DR, %	1.39	1.12	0.82	1.68
95% CI	0.96–2.00	0.67–1.82	0.38–1.68	0.91–3.01
Advanced adenomas PPV, %	34.5	31.5	27.6	33.3
95% CI	24.8–45.5	19.9–45.7	13.4–47.5	19.1–51.1
Cancer, n	5	1	2	0
Cancer DR, %	0.23	0.07	0.21	0
95% CI	0.09–0.57	0.00–0.43	0.04–0.83	
Cancer PPV, %	5.8	1.9	6.9	0
95% CI	2.1–13.5	0.1–11.2	1.2–24.1	

[a]Number of subjects who performed the indicated number of tests over 4 screening rounds, ie, 2161 of 2959 people performed at least one FIT between 2001 and 2008, 1520 of 2959 had 2 consecutive tests, and so forth.

of CRCs were detected among people with previous negative test results, whereas the PPV of FIT for advanced adenomas was not influenced by the number of previous negative test results. Because the stability of the PPV was associated with a similar trend in the positive rate, the detection rate of advanced adenomas remained considerably high over all rounds.

Although the small size of the study population represents a major limitation, the observed findings are consistent with the results of the Aosta Valley Region program,[4] which suggests that the cohort under study is representative of the entire screening population. Also, the results obtained for advanced adenomas in the first round in 2001 were similar, in terms of PPV (34.5%) and DR (1.39%), to those obtained in 2008 in Italy, with the same FIT at the same cut-off value, among 2,576,000 people invited for screening in 87 programs (30.3% and 1.31%, respectively).[4]

The high participation rate in our population likely is attributable to the adoption of a FIT performed on a single sample, without dietary restrictions, and to the involvement of GPs.[13,14] The AR achieved is higher than reported in many gFOBT programs: in the Scottish pilot study,[15] the AR ranged between 53% and 55% over 3 rounds, whereas in the Burgundy study,[13] it varied between 53% and 58% over 6 rounds. A high AR in each single round may not be sufficient, however, to achieve the expected health impact of screening, which is dependent on the participant's willingness to repeat testing at regular intervals. Longitudinal adherence of the same subject therefore represents a critical factor, but information concerning sustained attendance is lacking and still mainly based on reports from old clinical trials using gFOBT.[16] Our findings show that, even in the context of an established program achieving high participation, the proportion of regular compliers, attending all 4 rounds, is relatively lower than one could expect (48%). As long as the observed loss of compliance reduces the benefit of screening, additional efforts are needed to reinforce and maintain a subject's commitment to active and sustained participation over time. Also, although subjects' screening patterns show a high variability, which tends to increase

Table 3. Cumulative Number of Tests and Detection Rate of AN in Consecutive and NC Rounds

Tests	1	2	3	4	2 NC[a]	3 NC[b]	Total
People examined	2161	1520	971	713	132	107	2161
Number of tests[c]	2161	3040	2913	2852	264	321	5604[d]
Number of AN	35	18	10	12	1	0	76
Cumulative DR of AN, %[e]	1.6	2.5	2.9	3.5	3.5	3.5	3.5
Number examinations per 1 AN	62	169	291	259	264	NA	74[f]

NA, not applicable.
[a]There were 132 people who performed 2 FITs with a 4-year interval between the examinations.
[b]A total of 107 people performed 2 consecutive FITs and a third test either 4 years after the second consecutive FIT (n = 68) or 4 years before the first of 2 consecutive FITs (n = 39).
[c]Cumulative number of tests (ie, 3040 FITs were performed to screen 1520 people attending in 2 consecutive rounds; 2913 tests to screen 971 people attending in 3 consecutives rounds, and so forth).
[d]The numbers of tests in each column are not mutually exclusive (ie, the 1520 subjects attending 2 consecutive rounds are included among those 2161 performing one test).
[e]DR of AN (CRC + advanced adenoma) over attenders at least once.
[f]Average in 4 rounds.

Table 4. Distribution of Cancer by Stage at Diagnosis Among Attenders (at Least 1 Test) and Never Attenders

	Stage of CRC, n (%)				
	I	II	III	IV	Total
Screen detected	3 (37.5)	1 (12.5)	3 (37.5)	1 (12.5)	8
Interval CRCs	0	1 (20.0)	1 (20.0)	3 (60.0)	5
Other CRCs among those who attended at least once	1 (20.0)	2 (40.0)	0	2 (40.0)	5
Total attenders	4 (22.2)	4 (22.2)	4 (22.2)	6 (33.3)	18
Total never attenders	1 (7.1)	2 (14.3)	1 (7.1)	10 (71.4)	14

over time, little information is available about the protective effect of irregular testing. These data therefore represent an opportunity to gather useful information of practiced FIT screening patterns.

The stability of the PR in our cohort contrasts with the results of many gFOBT trials[13,15,16] reporting a decreasing trend from the first to the subsequent rounds. Only in the Danish trial[17] the PR increased from the initial to the last 4 rounds (respectively 1% and 1.8%). A reduction in PR over repeated screenings would be expected because the disease prevalence should be reduced as a result of an increasing proportion of screened patients having undergone previous negative tests. A possible explanation for the stability of the PR relates to the aging of our cohort, which might have masked the expected decrease in the PR, while the false-positive rate would remain stable over time.

The DR of advanced adenomas remained considerably higher in our cohort than in the gFOBT trials over all screening rounds, which suggests a higher sensitivity of the FIT for these lesions, as already reported.[5–9] The cumulative DR of advanced adenomas was higher after 4 FIT screening rounds in our study than after 8 gFOBT rounds in the Danish trial,[18] but still was lower than the yield of a single screening sigmoidoscopy.[19] Moreover, the observed trend in the DR of CRC and advanced adenomas would suggest that FIT led to the detection of most prevalent CRCs in the initial rounds, while in test-negative patients continued screening would be associated with the detection of the remaining advanced adenomas. Because the advanced adenomas generally are considered a precursor of CRC, these findings would indicate that repeated FIT testing might result in a higher CRC incidence reduction as compared with gFOBT screening. We calculated that 28 people need to be screened about 3 times (average, 2.6) over 4 rounds to detect 1 AN. The NNS to detect 1 AN in the prevalence round (NNS, 62) was much lower than estimates reported in a French[20] population program with gFOBT (NNS, 107).

Over the 8.5-year follow-up period, we registered a lower cumulative incidence and a more favorable stage distribution of CRCs detected among people attending screening at least once than among people who never attended. Even if the 2 populations showed a similar age and gender distribution, a direct comparison would be questionable. Indeed, nonparticipants may represent a self-selected group, less health-oriented, with a higher risk of CRC.[21,22] Moreover, the small sample size, together with the relatively short duration of the follow-up period, do not allow investigation and detection of changes in the incidence trends as a result of the screening program.

In conclusion, our findings suggest that in an organized screening setting with active invitation of the target population, the proportion of regular attenders in repeated rounds tends to decrease over time, even if the observed participation in each single round remains increased. As long as longitudinal adherence of the same subject is a critical component of the impact of FOBT screening, the results highlight the need for additional efforts to sustain individual participation over time. We registered a high DR of advanced adenomas, even after several negative test results, which suggests a higher impact of regular FIT testing on CRC incidence, as compared with gFOBT testing. Wider population studies are needed, however, to estimate the possible FIT protective effect over time among both regular and irregular attenders.

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Reprint requests

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This was an observational study monitoring the quality indicators of a fecal occult blood screening program, according to the guidelines approved by the World Health Organization and the Italian Health Ministry. At a local level, organizational, logistic, and performance indicators are monitored by a Technical Committee (approved by Regione Valle d'Aosta in 2005) and by the Centro Prevenzione Oncologica of Turin. In 2001, at the beginning of the program, the first screening protocol also was approved by the Regional Ethics Committee. Informed consent was always obtained from all subjects participating in all screening rounds. We disclosed potential investigator conflicts of interest to study participants.

Conflicts of interest

The authors disclose no conflicts.